

Appl. No. 10/651,690  
Response to Office Action June 27, 2007

Atty Dkt. No 112461-016

### Listing of Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claim 1 (currently amended): A method for treating infertility in a subject, the subject having a ratio of T helper 1 (Th1) immune response to T helper 2 (Th2) immune response, the method comprising withdrawing a blood sample from the subject prior to conception and measuring ~~an in-serum or intracellular~~ [a] Th1 immune response and ~~an in-serum or intracellular~~ [a] Th2 immune response, administering to the subject prior to conception a Th1 antagonist or a Th2 agonist to reduce the ratio of the Th1 immune response to the Th2 immune response in the subject to inhibit spontaneous abortion or implantation failure and withdrawing a blood sample from the subject after administering the Th1 antagonist or the Th2 agonist and measuring ~~an in-serum or intracellular~~ the Th1 immune response and ~~an in-serum or intracellular~~ the Th2 immune response, wherein the ratio of Th1 immune response to Th2 immune response in the subject is determined by measuring a ratio of the level of a Th1 cytokine to a level of a Th2 cytokine, wherein the method of reducing the ratio of the Th1 immune response to the Th2 immune response is achieved by suppressing the Th1 cytokines in the subject by administering an effective dose of a Th1 cytokine antagonist, wherein the Th1 cytokine antagonist is selected from a group consisting of IL-1 antagonists, IL-2 antagonists, TNF- $\alpha$  antagonists, and IFN- $\alpha$  antagonists, wherein the Th1 cytokines are selected from the group consisting of IL-1, IL-2, TNF- $\alpha$ , and IFN- $\gamma$ , and wherein the Th2 cytokines are selected from the group consisting of IL-4, IL-5, IL-6, and IL-10.

Claim 2 (previously presented): The method of claim 1, wherein the implantation failure occurs after assisted reproductive technology (ART) cycles or ovulation induction cycles.

Claim 3 (previously presented): The method of claim 2, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

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Claim 4 (currently amended): The method of claim 1, wherein the ratio of Th1 immune response to Th2 immune response in the subject is a ratio of absolute cell counts ~~or percentage~~ of a representative population of Th1 cells to a representative population of Th2 cells.

Claim 5 (canceled): The method of claim 1, wherein the ratio of Th1 immune response to Th2 immune response in the subject is determined by measuring a ratio of the level of a Th1 cytokine to a Th2 cytokine.

Claim 6 (currently amended): The method of claim 5[1], wherein the levels of Th1 and Th2 cytokines are serum levels.

Claim 7 (currently amended): The method of claim 5[1], wherein the levels of Th1 and Th2 cytokines are intracellular levels.

Claim 8 (currently amended): The method of claim 4 [4], wherein the method of reducing the ratio of Th1 immune response to Th2 immune response is to reduce the absolute counts of Th1 cells in the subject.

Claim 9 (previously presented): The method of claim 8, wherein the Th1 cell is a TNF- $\alpha$  or IFN- $\gamma$  expressing CD3+/CD4+ T-cell.

Claim 10 (currently amended): The method of claim 4[4], wherein the method of reducing the ratio of Th1 immune response to Th2 immune response is to increase the absolute counts of Th2 cells in the subject.

Claim 11 (previously presented): The method of claim 10, wherein the Th2 cell is an IL-4 or IL-10 expressing CD3+/CD8- T-cell.

Claim 12 (canceled): The method of claim 1, wherein the method of reducing the ratio of Th1 immune response to Th2 immune response is to suppress the Th1 cytokines in the subject.

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Claim 13 (original): The method of claim 1, wherein the method of reducing the ratio of Th1 immune response to Th2 immune response is to enhance the level of Th2 cytokines in the subject.

Claim 14 (canceled): The method of claim 12, wherein the Th1 cytokines are selected from the group consisting of IL-1, IL-2, TNF- $\alpha$ , and IFN- $\gamma$ .

Claim 15 (canceled): The method of claim 13, wherein the Th2 cytokines are selected from the group consisting of IL-4, IL-5, IL-6, IL-10.

Claim 16 (currently amended): The method of claim 5[1], wherein the Th1 to Th2 cytokine ratio is a ratio of IFN- $\gamma$  to IL-4.

Claim 17 (currently amended): The method of claim 5[1], wherein the Th1 to Th2 cytokine ratio is a ratio of IFN- $\gamma$  to IL-10.

Claim 18 (currently amended): The method of claim 5[1], wherein the Th1 to Th2 cytokine ratio is a ratio of TNF- $\alpha$  to IL-4.

Claim 19 (currently amended): The method of claim 5[1], wherein the Th1 to Th2 cytokine ratio is a ratio of TNF- $\alpha$  to IL-10.

Claim 20 (withdrawn): The method of claim 5, wherein the method of reducing the count of Th1 cells is by administering an effective dose of an inhibitor of a costimulatory signal of a T-cell.

Claim 21 (withdrawn): The method of claim 20, wherein the agent is an antibody to CD80.

Claim 22 (withdrawn): The method of claim 20, wherein the agent is an antibody to CD86.

Claim 23 (withdrawn): The method of claim 20, wherein the agent is an antibody to ICOS.

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Claim 24 (withdrawn): The method of claim 20, wherein the agent is a soluble form of CD28.

Claim 25 (withdrawn): The method of claim 20, wherein the agent is a soluble form of ICOS.

Claim 26 (withdrawn): The method of claim 20, wherein the agent is a soluble form of CTLA4.

Claim 27 (withdrawn): The method of claim 10, wherein the method of increasing the count of Th2 cells is by administering an effective dose of a T helper 2-immuno-stimulatory nucleic acid.

Claim 28 (canceled): The method of claim 12, wherein the method of suppressing the Th1 cytokines is by administering an effective dose of a Th1 cytokine antagonist to the subject.

Claim 29 (currently amended): The method of claim 28[1], wherein the Th1 cytokine antagonist is an inhibitor of the synthesis of the cytokine.

Claim 30 (currently amended): The method of claim 28[1], wherein the Th1 cytokine antagonist blocks the binding of the cytokine to its receptor.

Claim 31 (currently amended): The method of claim 28[1], wherein the Th1 cytokine antagonist inactivates the cytokine by binding to the cytokine.

Claim 32 (currently amended): The method of claim 28[1], wherein the Th1 cytokine antagonist is a polyclonal antibody.

Claim 33 (currently amended): The method of claim 28 [1], wherein the Th1 cytokine antagonist is a monoclonal antibody.

Claim 34 (currently amended): The method of claim 28[1], wherein the Th1 cytokine antagonist is a soluble receptor of the cytokine.

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Claim 35 (canceled): The method of claim 28, wherein the Th1 cytokine antagonist is selected from the group consisting of: IL-1 antagonists, IL-2 antagonists, TNF- $\alpha$  antagonists, and IFN- $\gamma$  antagonists.

Claim 36 (currently amended): The method of claim 35 [1], wherein the TNF- $\alpha$  antagonist is infliximab.

Claim 37 (currently amended): The method of claim 35 [1], wherein the TNF- $\alpha$  antagonist is etanercept.

Claim 38 (currently amended): The method of claim 35 [1], wherein the TNF- $\alpha$  antagonist is D2E7.

Claim 39 (currently amended): The method of claim 35 [1], wherein the TNF- $\alpha$  antagonist is CDP571.

Claim 40 (currently amended): The method of claim 35[1], wherein the TNF- $\alpha$  antagonist is CDP870.

Claim 41 (withdrawn): The method of claim 35, wherein the TNF- $\alpha$  antagonist is a thalidomide analog.

Claim 42 (withdrawn): The method of claim 35, wherein the TNF- $\alpha$  antagonist is a phosphodiesterase type IV inhibitor.

Claim 43 (original): The method of claim 1, wherein the treatment of infertility further comprises enhancing embryo implantation, pregnancy, or birth rates of the subject.

Claim 44 (original): The method of claim 1, wherein the treatment of infertility enhances the ability of the subject to carry at least one embryo to term.

Claim 45 (original): The method of claim 1, wherein the subject is a human.

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Claim 46 (original): The method of claim 1, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 47 (previously presented): The method of claim 46, wherein the implantation failures occur after ART cycles or ovulation induction cycles.

Claim 48 (previously presented): The method of claim 47, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 49 (original): The method of claim 1, wherein the subject undergoes natural conception.

Claim 50 (previously presented): The method of claim 1, wherein the subject undergoes ART cycles or ovulation induction cycles.

Claim 51 (previously presented): The method of claim 50, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 52 (original): The method of claim 1, wherein the subject undergoes ovulation induction cycles.

Claim 53 (currently amended): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising withdrawing a blood sample from the subject prior to conception and measuring ~~an in serum or intracellular~~ [a] Th1 immune response and ~~an in serum or intracellular~~ [a] Th2 immune response and administering a therapeutically effective dosage level of a TNF- $\alpha$  antagonist to the subject prior to conception by the subject and withdrawing a blood sample from the subject after administering the TNF- $\alpha$  antagonist and measuring ~~an in serum or intracellular~~ [a] Th1 immune response and ~~an in serum or intracellular~~ [a] Th2 immune response, wherein the ratio of Th1 immune response to Th2 immune response in the subject is determined by measuring a ratio of the level of a Th1 cytokine to a Th2

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cytokine, wherein the Th1 cytokines are selected from the group consisting of IL-1, IL-2, TNF- $\alpha$ , and IFN- $\gamma$ , and wherein the Th2 cytokines are selected from the group consisting of IL-4, IL-5, IL-6, and IL-10.

Claim 54 (original): The method of claim 53, wherein the implantation failure occurs after ART cycles.

Claim 55 (previously presented): The method of claim 54, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 56 (original): The method of claim 53, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 57 (original): The method of claim 53, wherein the subject is a human.

Claim 58 (original): The method of claim 53, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 59 (original): The method of claim 58, wherein the implantation failures occur after ART cycles.

Claim 60 (previously presented): The method of claim 59, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 61 (original): The method of claim 53, wherein the subject undergoes natural conception.

Claim 62 (original): The method of claim 53, wherein the subject undergoes ART cycles.

Claim 63 (previously presented): The method of claim 62, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.



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Claim 64 (original): The method of claim 53, wherein the subject undergoes ovulation induction cycles.

Claim 65 (original): The method of claim 53, wherein the TNF- $\alpha$  antagonist is infliximab.

Claim 66 (original): The method of claim 53, wherein the TNF- $\alpha$  antagonist is etanercept.

Claim 67 (original): The method of claim 53, wherein the TNF- $\alpha$  antagonist is D2E7.

Claim 68 (original): The method of claim 53, wherein the TNF- $\alpha$  antagonist is CDP571.

Claim 69 (original): The method of claim 53, wherein the TNF- $\alpha$  antagonist is CDP870.

Claim 70 (withdrawn): The method of claim 53, wherein the TNF- $\alpha$  antagonist is a thalidomide analog.

Claim 71 (withdrawn): The method of claim 53, wherein the TNF- $\alpha$  antagonist is a phosphodiesterase type IV inhibitor.

Claim 72 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the composition comprising a TNF- $\alpha$  antagonist formulated in a formulation suitable for administration to the subject vaginally.

Claim 73 (currently amended): A method of enhancing the ability of a subject to carry at least one embryo to term comprising withdrawing a blood sample from the subject prior to conception and measuring ~~an in serum or intracellular~~ [a] Th1 immune response and ~~an in serum or intracellular~~ [a] Th2 immune response and administering to the subject prior to conception by the subject an effective dose of a TNF- $\alpha$  antagonist to



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inhibit TNF- $\alpha$  in the subject to inhibit spontaneous abortion or implantation failure and withdrawing a blood sample from the subject after administering the TNF- $\alpha$  antagonist and measuring ~~an in-serum or intracellular~~ [a] Th1 immune response and ~~an in-serum or intracellular~~ [a] Th2 immune response, wherein the ratio of Th1 immune response to Th2 immune response in the subject is determined by measuring a ratio of the level of a Th1 cytokine to a Th2 cytokine, wherein the Th1 cytokines are selected from the group consisting of IL-1, IL-2, TNF- $\alpha$ , and IFN- $\gamma$ , and wherein the Th2 cytokines are selected from the group consisting of IL-4, IL-5, IL-6, and IL-10.

Claim 74 (original): The method of claim 73, wherein the implantation failure occurs after ART cycles.

Claim 75 (previously presented): The method of claim 74, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 76 (original): The method of claim 73, wherein the subject is a human.

Claim 77 (original): The method of claim 73, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 78 (original): The method of claim 73, wherein the TNF- $\alpha$  antagonist is infliximab.

Claim 79 (original): The method of claim 73, wherein the TNF- $\alpha$  antagonist is etanercept.

Claim 80 (original): The method of claim 73, wherein the TNF- $\alpha$  antagonist is D2E7.

Claim 81 (original): The method of claim 73, wherein the TNF- $\alpha$  antagonist is CDP571.

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Claim 82 (previously presented): The method of claim 73, wherein the TNF- $\alpha$  antagonist is CDP870.

Claim 83 (withdrawn): The method of claim 73, wherein the TNF- $\alpha$  antagonist is a thalidomide analog.

Claim 84 (withdrawn): The method of claim 73, wherein the TNF- $\alpha$  antagonist is a phosphodiesterase type IV inhibitor.

Claim 85 (withdrawn): A pharmaceutical composition for enhancing the ability of a subject to carry at least one embryo to term comprising a TNF- $\alpha$  antagonist to inhibit TNF- $\alpha$  in the subject to inhibit spontaneous abortion or implantation failure, wherein the TNF- $\alpha$  is formulated in formulation suitable for administration to the subject vaginally.

Claim 86 (previously presented): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of infliximab to the subject prior to conception by the subject.

Claim 87 (original): The method of claim 86, wherein the implantation failure occurs after ART cycles.

Claim 88 (previously presented): The method of claim 86, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 89 (original): The method of claim 86, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 90 (original): The method of claim 86, wherein the subject is a human.

Claim 91 (original): The method of claim 86, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

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Claim 92 (original): The method of claim 91, wherein the implantation failures occur after ART cycles.

Claim 93 (previously presented): The method of claim 92, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 94 (original): The method of claim 86, wherein the subject undergoes natural conception.

Claim 95 (original): The method of claim 86, wherein the subject undergoes ART cycles.

Claim 96 (previously presented): The method of claim 95, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 97 (original): The method of 86, wherein the subject undergoes ovulation induction cycles.

Claim 98 (original): The method of claim 86, wherein the therapeutically effective dosage level of infliximab is from about 3 mg/Kg to about 10 mg/Kg.

Claim 99 (original): The method of claim 86, wherein the administration of infliximab is performed by delivering a therapeutically effective dosage level of infliximab intravenously.

Claim 100 (original): The method of claim 86, wherein the administration of infliximab is performed by delivering a therapeutically effective dosage level of infliximab subcutaneously.

Claim 101 (original): The method of claim 86, wherein the administration of infliximab is performed by delivering a therapeutically effective dosage level of infliximab vaginally.

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Claim 102 (original): The method of claim 101, wherein the infliximab is in a gel form.

Claim 103 (original): The method of claim 86, wherein the administration of infliximab is performed by delivering a therapeutically effective dosage of infliximab at least once prior to index conception cycle day one.

Claim 104 (original): The method of claim 86, wherein the step of the administration of infliximab is performed by delivering a therapeutically effective dosage of infliximab at least once on index conception cycle day one.

Claim 105 (original): The method of claim 86, wherein the administration of infliximab is performed by delivering a therapeutically effective dosage of infliximab at least once after index conception cycle day one.

Claim 106 (original): The method of claim 86, wherein the subject further receives lymphocyte immunization or autoimmune treatment.

Claim 107 (original): The method of claim 86, wherein the subject further receives intravenous immunoglobulin G.

Claim 108 (original): The method of claim 86, wherein the subject further receives at least one anticoagulant.

Claim 109 (original): The method of claim 108, wherein one of the anticoagulants is heparin.

Claim 110 (original): The method of claim 108, wherein one of the anticoagulants is aspirin.

Claim 111 (original): The method of claim 86, wherein the subject further receives prednisone.

Claim 112 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo

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implantation, pregnancy, or birth rates, the composition comprising infliximab formulated in a formulation suitable for administration to the subject vaginally prior to conception by the subject.

Claim 113 (previously presented): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of etanercept to the subject prior to conception by the subject.

Claim 114 (original): The method of claim 113, wherein the implantation failure occurs after ART cycles.

Claim 115 (previously presented): The method of claim 114, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 116 (original): The method of claim 113, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 117 (original): The method of claim 113, wherein the subject is a human.

Claim 118 (original): The method of claim 113, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 119 (original): The method of claim 118, wherein the implantation failures occur after ART cycles.

Claim 120 (previously presented): The method of claim 119, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 121 (original): The method of claim 113, wherein the subject undergoes natural conception.

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Claim 122 (original): The method of claim 113, wherein the subject undergoes ART cycles.

Claim 123 (previously presented): The method of claim 122, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 124 (original): The method of claim 113, wherein the subject undergoes ovulation induction cycles.

Claim 125 (original): The method of claim 113, wherein the therapeutically effective dosage level of etanercept is from about 3 mg to about 50 mg.

Claim 126 (original): The method of claim 113, where the administration of etanercept is performed by delivering a therapeutically effective dosage level of etanercept subcutaneously.

Claim 127 (original): The method of claim 113, wherein the administration of etanercept is performed by delivering a therapeutically effective dosage level of etanercept vaginally.

Claim 128 (original): The method of claim 127, wherein the etanercept is in a gel form.

Claim 129 (original): The method of claim 113, wherein the administration of etanercept is performed by delivering a therapeutically effective dosage of etanercept at least once prior to index conception cycle day one.

Claim 130 (previously presented): The method of claim 113, wherein the administration of etanercept is performed by further delivering a therapeutically effective dosage of etanercept at least once on index conception cycle day one.

Claim 131 (previously presented): The method of claim 113, wherein the administration of etanercept is performed by further delivering a therapeutically effective dosage of etanercept at least once after index conception cycle day one.

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Claim 132 (original): The method of claim 113, wherein the subject further receives lymphocyte immunization or autoimmune treatment.

Claim 133 (original): The method of claim 113, wherein the subject further receives intravenous immunoglobulin G.

Claim 134 (original): The method of claim 113, wherein the subject further receives at least one anticoagulant.

Claim 135 (original): The method of claim 134, wherein one of the anticoagulants is heparin.

Claim 136 (original): The method of claim 134, wherein one of the anticoagulants is aspirin.

Claim 137 (original): The method of claim 113, wherein the subject further receives prednisone.

Claim 138 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the composition comprising etanercept formulated in a formulation suitable for administration to the subject vaginally.

Claim 139 (previously presented): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of D2E7 to the subject prior to conception by the subject.

Claim 140 (original): The method of claim 139, wherein the implantation failure occurs after ART cycles.

Claim 141 (previously presented): The method of claim 140, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.



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Claim 142 (original): The method of claim 139, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 143 (original): The method of claim 139, wherein the subject is a human.

Claim 144 (original): The method of claim 139, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 145 (original): The method of claim 144, wherein the implantation failures occur after ART cycles.

Claim 146 (currently amended): The method of claim 145, wherein the ART is includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 147 (original): The method of claim 139, wherein the subject undergoes natural conception.

Claim 148 (original): The method of claim 139, wherein the subject undergoes ART cycles.

Claim 149 (previously presented): The method of claim 148, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 150 (original): The method of claim 139, wherein the subject undergoes ovulation induction cycles.

Claim 151 (currently amended): The method of claim 124, wherein the dosage level of ~~D2E7~~ etanercept is from about 5 mg to about 50 mg.

Claim 152 (original): The method of claim 139, wherein the administration of D2E7 is performed by delivering a therapeutically effective dosage level of D2E7 subcutaneously.

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Claim 153 (original): The method of claim 139, wherein the administration of D2E7 is performed by delivering a therapeutically effective dosage level of D2E7 intravenously.

Claim 154 (original): The method of claim 139, wherein the administration of D2E7 is performed by delivering a therapeutically effective dosage level of D2E7 vaginally.

Claim 155 (original): The method of claim 139, wherein the administration of D2E7 is performed by delivering a therapeutically effective dosage of D2E7 at least once prior to index conception cycle day one.

Claim 156 (previously presented): The method of claim 139, wherein the administration of D2E7 is performed by further delivering a therapeutically effective dosage of D2E7 at least once on index conception cycle day one.

Claim 157 (previously presented): The method of claim 139, wherein the administration of D2E7 is performed by further delivering a therapeutically effective dosage of D2E7 at least once after index conception cycle day one.

Claim 158 (original): The method of claim 139, wherein the subject further receives lymphocyte immunization or autoimmune treatment.

Claim 159 (original): The method of claim 139, wherein the subject further receives intravenous immunoglobulin G.

Claim 160 (original): The method of claim 139, wherein the subject further receives at least one anticoagulant.

Claim 161 (original): The method of claim 160, wherein one of the anticoagulants is heparin.

Claim 162 (original): The method of claim 160, wherein one of the anticoagulants is aspirin.

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Claim 163 (original): The method of claim 139, wherein the subject further receives prednisone.

Claim 164 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the composition comprising D2E7 formulated in a formulation suitable for administration to the subject vaginally.

Claim 165 (previously presented): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of CDP571 to the subject prior to conception by the subject.

Claim 166 (original): The method of claim 165, wherein the implantation failure occurs after ART cycles.

Claim 167 (previously presented): The method of claim 166, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 168 (original): The method of claim 165, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 169 (original): The method of claim 165, wherein the subject is a human.

Claim 170 (original): The method of claim 165, wherein the subject has had one or more previous spontaneous abortions, or implantation failures.

Claim 171 (original): The method of claim 170, wherein the implantation failures occur after ART cycles.

Claim 172 (previously presented): The method of claim 171, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

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Claim 173 (original): The method of claim 170, wherein the subject undergoes natural conception.

Claim 174 (original): The method of claim 165, wherein the administration of CDP571 is performed by delivering a therapeutically effective dosage level of CDP571 subcutaneously.

Claim 175 (original): The method of claim 165, wherein the administration of CDP571 is performed by delivering a therapeutically effective dosage level of CDP571 vaginally.

Claim 176 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the composition comprising CDP571 formulated in a formulation suitable for administration to the subject vaginally.

Claim 177 (previously presented): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of CDP870 to the subject prior to conception by the subject.

Claim 178 (original): The method of claim 177, wherein the implantation failure occurs after ART cycles.

Claim 179 (previously presented): The method of claim 178, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 180 (original): The method of claim 177, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 181 (original): The method of claim 177, wherein the subject is a human.

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Claim 182 (original): The method of claim 177, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 183 (original): The method of claim 177, wherein the subject undergoes natural conception.

Claim 184 (original): The method of claim 182, wherein the implantation failures occur after ART cycles.

Claim 185 (previously presented): The method of claim 184, wherein the ART includes all fertility treatments in which both eggs and sperm are handled including in vitro fertilization.

Claim 186 (original): The method of claim 177, wherein the administration of CDP870 is performed by delivering a therapeutically effective dosage level of CDP870 subcutaneously.

Claim 187 (original): The method of claim 177, wherein the administration of CDP870 is performed by delivering a therapeutically effective dosage level of CDP870 vaginally.

Claim 188 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the composition comprising CDP870 formulated in a formulation suitable for administration to the subject vaginally.

Claim 189 (withdrawn): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of a thalidomide analog to the subject.

Claim 190 (withdrawn): The method of claim 189, wherein the implantation failure occurs after ART cycles.

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Claim 191 (withdrawn): The method of claim 190, where in the ART is in vitro fertilization

Claim 192 (withdrawn): The method of claim 189, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 193 (withdrawn): The method of claim 189, wherein the subject is a human.

Claim 194 (withdrawn): The method of claim 189, wherein the subject undergoes natural conception.

Claim 195 (withdrawn): The method of claim 189, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 196 (withdrawn): The method of claim 194, wherein the implantation failures occur after ART cycles.

Claim 197 (withdrawn): The method of claim 196, wherein the ART is in vitro fertilization.

Claim 198 (withdrawn): The method of claim 189, wherein the administration of the thalidomide analog is performed by delivering a therapeutically effective dosage level of the thalidomide analog orally, vaginally, subcutaneously or intravenously.

Claim 199 (withdrawn): The method of claim 189, wherein the administration of the thalidomide analog is performed subcutaneously in the woman wherein the dosage level is from about 50 mg/Kg to about 800 mg/Kg.

Claim 200 (withdrawn): The method of claim 189, wherein the therapeutically effective dosage level is sufficient to produce a blood level of the thalidomide analog of at least 0.1 µg/ml.

Claim 201 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failures for enhancing embryo

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implantation, pregnancy, or birth rates, the composition comprising a thalidomide analog formulated in a formulation suitable for administration to the subject vaginally.

Claim 202 (withdrawn): A method for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo implantation, pregnancy, or birth rates, the method comprising administering a therapeutically effective dosage level of a phosphodiesterase type IV inhibitor to the subject.

Claim 203 (withdrawn): The method of claim 202, wherein the implantation failure occurs after ART cycles.

Claim 204 (withdrawn): The method of claim 203, wherein the ART is in vitro fertilization cycles.

Claim 205 (withdrawn): The method of claim 202, further enhancing the ability of the subject to carry at least one embryo to term.

Claim 206 (withdrawn): The method of claim 202, wherein the subject undergoes natural conception.

Claim 207 (withdrawn): The method of claim 202, wherein the subject is a human.

Claim 208 (withdrawn): The method of claim 202, wherein the subject has had one or more previous spontaneous abortions or implantation failures.

Claim 209 (withdrawn): The method of claim 208, wherein implantation failures occur after ART cycles.

Claim 210 (withdrawn): The method of claim 209, wherein the ART is in vitro fertilization.

Claim 211 (withdrawn): A pharmaceutical composition for treating infertility in a subject by inhibiting spontaneous abortion or implantation failure for enhancing embryo



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implantation, pregnancy, or birth rates, the composition comprising a phosphodiesterase type IV inhibitor formulated in a formulation suitable for administration to the subject vaginally.

Claim 212 (withdrawn): A method for diagnosing infertility in a subject with recurrent spontaneous abortions or one or more implantation failures comprising determining a ratio of Th1 and Th2 immune responses of the subject and comparing the ratio with that from subjects with normal pregnancies to determine if the subject is at risk of infertility or if the subject is suitable for treatment of the infertility by reducing ratio of Th1 to Th2 immune responses in the subject.

Claim 213 (withdrawn): The method of claim 212, wherein the implantation failures occur after ART cycles.

Claim 214 (withdrawn): The method of claim 213, wherein the ART is in vitro fertilization.

Claim 215 (withdrawn): The method of claim 212, wherein the Th1 immune response is measured by the absolute cell counts of Th1 cytokine expressing T-cells, and the Th2 immune response is measured by the absolute cell counts of Th2 cytokine expressing T-cells.

Claim 216 (withdrawn): The method of claim 215, wherein the Th1 and Th2 immune responses are measured by flow cytometry analysis.

Claim 217 (withdrawn): The method of claim 215, wherein the Th1 cytokine expressing T-cell is a TNF- $\alpha$  expressing CD3+/CD4+ T-cell.

Claim 218 (withdrawn): The method of claim 215, wherein the Th2 cytokine expressing T-cell is a IL-4 expressing CD3+/CD4+ T-cell.

Claim 219 (withdrawn): The method of claim 212, wherein the ratio of Th1 immune response to Th2 immune response is a ratio of the levels of Th1 and Th2 cytokines.

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Claim 220 (withdrawn): The method of claim 219, wherein the levels of Th1 and Th2 cytokines are serum levels.

Claim 221 (withdrawn): The method of claim 219, wherein the levels of Th1 and Th2 cytokines are intracellular levels.

Claim 222 (withdrawn): The method of claim 219, wherein the Th1 cytokine is IL-1.

Claim 223 (withdrawn): The method of claim 219, wherein the Th1 cytokine is IL-2.

Claim 224 (withdrawn): The method of claim 219, wherein the Th1 cytokine is TNF- $\alpha$ .

Claim 225 (withdrawn): The method of claim 219, wherein the Th1 cytokine is IFN- $\gamma$ .

Claim 226 (withdrawn): The method of claim 219, wherein the Th2 cytokine is IL-4.

Claim 227 (withdrawn): The method of claim 219, wherein the Th2 cytokine is IL-5.

Claim 228 (withdrawn): The method of claim 219, wherein the Th2 cytokine is IL-6.

Claim 229 (withdrawn): The method of claim 219, wherein the Th2 cytokine is IL-10.

Claim 230 (withdrawn): The method of claim 219, wherein the Th1 to Th2 cytokine ratio is the ratio of IFN- $\gamma$  to IL-4.

Claim 231 (withdrawn): The method of claim 219, wherein the Th1 to Th2 cytokine ratio is the ratio of IFN- $\gamma$  to IL-10.

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Claim 232 (withdrawn): The method of claim 219, wherein the Th1 to Th2 cytokine ratio is the ratio of TNF- $\alpha$  to IL-4.

Claim 233 (withdrawn): The method of claim 219, wherein the Th1 to Th2 cytokine ratio is the ratio of TNF- $\alpha$  to IL-10.

Claim 234 (withdrawn): A diagnostic kit for diagnosing infertility with recurrent spontaneous abortions or one or more implantation failure in a subject, the kit comprising:

- (a) means for determining Th1 immune response; and
- (b) means for determining Th2 immune response.

Claim 235 (withdrawn): The diagnostic kit of claim 234, wherein the implantation failures occur after ART cycles.

Claim 236 (withdrawn): The diagnostic kit of claim 235, wherein the ART is in vitro fertilization.

Claim 237 (withdrawn): The diagnostic kit of claim 234, further providing a ratio of Th1 to Th2 immune responses in a population of other subjects with normal pregnancies.

Claim 238 (withdrawn): The diagnostic kit of claim 234, wherein the Th1 immune response is the levels of Th1 cytokines in the subject, the means for determining the Th1 immune response comprises a Th1 cytokine antibody, the Th2 immune response is the levels of Th2 cytokines in the subject, and the means for determining the Th2 immune response comprises a Th2 cytokine antibody.

Claim 239 (withdrawn): The diagnostic kit of claim 234, wherein the antibody is a polyclonal or monoclonal antibody or a fragment thereof.

Claim 240 (withdrawn): A method for determining whether a treatment of infertility in a subject with recurrent spontaneous abortions or one or more implantation failures by reducing the ratio of Th1 to Th2 immune responses is having the desired

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effect of enhancing embryo implantation, pregnancy, or birth rates in the subject, the method comprising the steps of:

- (a) determining the ratio of the level of Th1 immune response to the level of Th2 immune response of the subject before the treatment;
- (b) determining the ratio of the level of Th1 immune response to the level of Th2 immune response of the subject after the treatment;
- (c) determining whether the ratio of Th1 to Th2 immune responses in the subject after the treatment is lower than that in the subject before the treatment to determine if the treatment has the desired effect.

Claim 241 (withdrawn): The method of claim 240, wherein the implantation failures occur after ART cycles.

Claim 242 (withdrawn): The method of claim 241, wherein the ART is in vitro fertilization.

Claim 243 (withdrawn): The method of claim 240, wherein the Th1 immune response is measured by the absolute cell counts of Th1 cytokine expressing T-cells and the Th2 immune response is measured by the absolute cell counts of Th2 cytokine expressing T-cells.

Claim 244 (withdrawn): The method of claim 243, wherein the Th1 and Th2 immune responses are measured by flow cytometry analysis.

Claim 245 (withdrawn): The method of claim 243, wherein the Th1 cytokine expressing T-cell is a TNF- $\alpha$  expressing CD3+/CD4+ T-cell.

Claim 246 (withdrawn): The method of claim 243, wherein the Th2 cytokine expressing T-cell is a IL-4 expressing CD3+/CD4+ T-cell.

Claim 247 (withdrawn): The method of claim 243, wherein the ratio of Th1 immune response to Th2 immune response is a ratio of the level of Th1 and Th2 cytokines.

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Claim 248 (withdrawn): The method of claim 247, wherein the levels of Th1 and Th2 cytokines are serum levels.

Claim 249 (withdrawn): The method of claim 247, wherein the levels of Th1 and Th2 cytokines are intracellular levels.

Claim 250 (withdrawn): The method of claim 247, wherein the Th1 cytokine is IL-1.

Claim 251 (withdrawn): The method of claim 247, wherein the Th1 cytokine is IL-2.

Claim 252 (withdrawn): The method of claim 247, wherein the Th1 cytokine is TNF- $\alpha$ .

Claim 253 (withdrawn): The method of claim 247, wherein the Th1 cytokine is IFN- $\gamma$ .

Claim 254 (withdrawn): The method of claim 247, wherein the Th2 cytokine is IL-4.

Claim 255 (withdrawn): The method of claim 247, wherein the Th2 cytokine is IL-5.

Claim 256 (withdrawn): The method of claim 247, wherein the Th2 cytokine is IL-6.

Claim 257 (withdrawn): The method of claim 247, wherein the Th2 cytokine is IL-10.

Claim 258 (withdrawn): A diagnostic method for determining whether a TNF- $\alpha$  antagonist therapy will likely enhance embryo implantation, pregnancy, or birth rates in a subject with recurrent spontaneous abortions or one or more implantation failures, the method comprising:

(a) measuring a level of TNF- $\alpha$  in the subject;

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(b) determining whether the level of TNF- $\alpha$  in the subject is higher than that in other subjects with normal pregnancies.

Claim 259 (withdrawn): The method of claim 258, wherein the implantation failures occur after ART cycles.

Claim 260 (withdrawn): The method of claim 259, wherein the ART is in vitro fertilization.

Claim 261 (withdrawn): The method of claim 258, wherein the level of TNF- $\alpha$  is determined by a method using a TNF- $\alpha$  antibody.

Claim 262 (withdrawn): The method of claim 261, wherein the antibody is a polyclonal or monoclonal antibody or a fragment thereof.

Claim 263 (withdrawn): The method of claim 258, wherein the level of TNF- $\alpha$  is serum level.

Claim 264 (withdrawn): The method of claim 263, wherein the serum level of TNF- $\alpha$  of the subject is considered higher than the level in other subjects with normal pregnancies when the level in the subject is higher than 12 pg/ml.

Claim 265 (withdrawn): The method of claim 258, wherein the level of TNF- $\alpha$  is intracellular level.

Claim 266 (withdrawn): A diagnostic kit of claim 258, comprising a means for measuring the level of TNF- $\alpha$ .

Claim 267 (withdrawn): The diagnostic kit of claim 266, wherein the means for measuring the level of TNF- $\alpha$  is an antibody.

Claim 268 (withdrawn): The diagnostic kit of claim 267, wherein the antibody is a polyclonal or a monoclonal antibody or a fragment thereof.

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Claim 269 (withdrawn): A method for determining whether a TNF- $\alpha$  antagonist treatment of infertility in a subject with recurring spontaneous abortions or one or more implantation failures is having the desired effect of enhancing embryo implantation, pregnancy, or birth rates in the subject, the method comprising the steps of:

- (a) measuring the level of TNF- $\alpha$  in the subject before the TNF- $\alpha$  antagonist treatment;
- (b) measuring the level of TNF- $\alpha$  in the subject after the TNF- $\alpha$  antagonist treatment;
- (c) determining whether the level of TNF- $\alpha$  in the subject after the TNF- $\alpha$  antagonist treatment is lower than that in the subject before the treatment.

Claim 270 (withdrawn): The method of claim 269, wherein the implantation failures occur after ART cycles.

Claim 271 (withdrawn): The method of claim 270, wherein the ART is in vitro fertilization.

Claim 272 (withdrawn): The method of claim 269, wherein the level of TNF- $\alpha$  is serum level.

Claim 273 (withdrawn): The method of claim 269, wherein the level of TNF- $\alpha$  is intracellular level.

Claim 274 (withdrawn): A diagnostic kit of claim 269, comprising a means for measuring the level of TNF- $\alpha$ .

Claim 275 (withdrawn): The diagnostic kit of claim 274, wherein the means for measuring the level of TNF- $\alpha$  is an antibody.

Claim 276 (withdrawn): The diagnostic kit of claim 275, wherein the antibody is a polyclonal or monoclonal antibody or a fragment thereof.



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Claim 277 (previously presented): The method of claim 1, wherein the step of reducing the ratio of the Th1 immune response to the Th2 immune response is by vaginal delivery of a TNF- $\alpha$  antagonist.

Claim 278 ~~288~~ (previously presented): The method of claim 53, wherein the TNF- $\alpha$  antagonist is delivered vaginally.

Claim 279-~~289~~ (previously presented): The method of claim 73, wherein the TNF- $\alpha$  antagonist is delivered vaginally.

Claim 280 ~~290~~ (previously presented): The method of claim 86, wherein the infliximab is delivered vaginally.

Claim 281 ~~291~~ (previously presented): The method of claim 139, wherein the D2E7 is delivered vaginally.

Claim 282 ~~292~~ (previously presented): The method of claim 165, wherein the CDP 571 is delivered vaginally.

Claim 283 ~~293~~ (previously presented): The method of claim 177, wherein the CDP870 is delivered vaginally.